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# Drug-Related Mortality and Fatal Overdose Risk: Pilot Cohort Study of Heroin Users Recruited From Specialist Drug Treatment Sites in London

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**ABSTRACT** *Fatal overdose and drug-related mortality are key harms associated with heroin use, especially injecting drug use (IDU), and are a significant contribution to premature mortality among young adults. Routine mortality statistics tend to underreport the number of overdose deaths and do not reflect the wider causes of death associated with heroin use. Cohort studies could provide evidence for interpreting trends in routine mortality statistics and monitoring the effectiveness of strategies that aim to reduce drug-related deaths. We aimed to conduct a retrospective mortality cohort study of heroin users recruited from an anonymous reporting system from specialist drug clinics. Our focus was to test whether (1) specialist agencies would agree to participate with a mortality cohort study, (2) a sample could be recruited to achieve credible estimates of the mortality rate, and (3) ethical considerations could be met. In total, 881 heroin users were recruited from 15 specialist drug agencies. The overall mortality rate of the cohort of heroin users was 1.6 (95% confidence interval [CI], 1.1 to 2.2) per 100 person-years. Mortality was higher among males, heroin users older than 30 years, and injectors, but not significantly higher after adjustment in a Cox proportional hazard model. Among the 33 deaths, 17 (52%) were certified from a heroin/methadone or opiate overdose, 4 (12%) from drug misuse, 4 (12%) unascertained, and 8 (24%) unrelated to acute toxic effects of drug use. Overall, the overdose mortality rate was estimated to be at least 1.0 per 100 person-years. The standardized mortality ratio (SMR) was 17 times higher for female and male heroin users in the cohort compared to mortality in the non-heroin-using London population aged 15–59 years. The pilot study showed that these studies are feasible and ethical, and that specialist drug agencies could have a vital role to play in the monitoring of drug-related mortality.*

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## INTRODUCTION

Drug-related mortality is a key harm associated with drug use and a key epidemiological variable for monitoring the prevalence of injecting drug use (IDU).[1,2] In the United Kingdom, reducing drug-related deaths has been adopted as a performance target to monitor progress of the government's drug strategy.[3] It has been estimated that the risk of death among injectors is over 10 times higher than for the general population, with the risk of fatal overdose estimated to be 0.8% per annum.[4] In England, overdose is a far greater cause of death among injectors than human immunodeficiency virus (HIV) infection[5] and is responsible for 6%–10% of general mortality among young people aged 15–34 years.[6] During the 1990s, the number of opiate overdose deaths more than doubled,[6,7] from fewer than 400 in 1993 to nearly 1,000 in 2000. Monitoring drug-related mortality may be improved by the development of methods that use information on both the number of opiate overdose deaths recorded by mortality statistics and the overdose mortality rate of injectors to estimate the size of the IDU population.[2,8]

There are two ways to monitor drug-related mortality. First, rates and trends in certified deaths due to drug misuse or poisoning are presented and analyzed, such as comparing trends in methadone-related and heroin-related deaths or describing geographical differences.[6,9,10] Second, cohort studies can be used to examine and monitor overall and cause-specific death rates among known IDUs.[11–17]

In practice, both types of information are needed to increase the evidence base and inform public health action to prevent drug-related mortality. Routine mortality statistics give only a partial picture of drug-related deaths as they tend to underestimate the number of drug-related overdose deaths, lack information on the drug misuser (such as whether they were an injector), and fail to identify other deaths associated with drug misuse, such as violence, suicide, and infectious diseases. Cohort studies can complete and complement the picture by providing information on a wider range of deaths.[18]

In addition, cohort studies can help interpret changes in mortality statistics trends and monitor prevention strategies. They can test whether an increase in the recorded number of overdose deaths was due to a change in the mortality rate of opiate users or IDUs or could be due to other reasons, such as changes in the population of drug users. Cohort studies can also test whether the risk of death from heroin overdose has decreased.

Despite the potential of these studies, few cities and countries maintain ongoing cohort studies of injectors to monitor drug-related mortality. The United Kingdom is perhaps unique. From 1968 to 1993, over 90,000 addicts in the Addicts Index were linked with death entries at the Office for National Statistics (ONS).[19,20] These studies suggested that the risk of mortality had fallen from approximately 2% in addicts notified during the 1967–1976 decade to 1% during the 1984–1993 decade. The termination of the Addicts Index in 1993 meant that such large-scale monitoring ceased.[21]

This was a pilot study of whether the Drug Misuse Database (DMD), a drug treatment monitoring system that replaced the Addicts Index, could be used to monitor mortality among heroin users and inform interpretation of routine mortality statistics. The DMD contains reports of clients with drug misuse problems that present to specialist drug treatment agencies.[22] For example, in London over 150 agencies reported more than 12,000 problem drug users to the DMD in 1999. The DMD collects "anonymous" attributes (initials, date of birth, and sex) to identify

duplicate reports, which are insufficient to allow direct record linkage with the ONS to flag and identify deaths. Instead, we decided to use the DMD as a sampling frame to select cases for inclusion in a cohort study. Success of the pilot study was measured in three ways: (1) whether specialist agencies would agree to participate in a mortality cohort study; (2) whether a sample could be recruited and flagged with the ONS and achieve credible estimates of the mortality rate; (3) whether ethical considerations of the specialist drug agencies and national and European guidelines on confidentiality could be met.

## METHODS

A range of specialist drug agencies from the statutory and nonstatutory sectors in North and South London and Brighton, including community, hospital, and residential services, were approached and asked to participate in the pilot study. These agencies were specifically selected from a list of 50 agencies that had reported more than 150 cases between 1997 and 1999. The total number of agencies and sample of problem drug users recruited were dictated by the limited time and resources available for the pilot.

To protect patient confidentiality and avoid deductive disclosure, the following design was agreed on through discussion with the specialist drug agencies and review and approval from ONS and the North Thames Multicenter Research Ethics Committee.

First, a random sample of reports to the DMD by the participating agencies for 1997 to 1999 was selected. The sample comprised reports of problem drug users whose main problem drug was heroin and who were reported for the first time to the DMD between 1997 and 1999. Client initials, date of birth, and a study number were copied to an ONS postcard and sent to each participating agency. When data are unable to be provided electronically, ONS provides postcards for matching with death entries, which are batched and posted in an envelope through registered mail.

Second, the agency retrieved the clients' records and added the full name, pseudonyms, date of birth, and address to the same postcard and returned it to ONS. Third, ONS attempted to match the data entered on the postcards with the National Health Service (NHS) Central Register, which holds details of all persons registered currently or previously with any NHS general practitioner and includes the health authority of current registration, emigration, or date of death for patients no longer registered. Finally, after copies of the death certificate with the person's name and address were removed and replaced by the study number, the information was sent back to the researchers.

Therefore, the postcard lacked any reference to the specialist drug agency or to drug use seen by administrators who worked on the matching at ONS. In addition, the copy of the death entry and list of persons matched to the central NHS register excluded the person's name and address.

Overall mortality and overdose mortality were estimated for all cases, with the follow-up period ending at death or finally censored at January 31, 2001. This cutoff point was selected on the advice of ONS to capture all death entries for the sample as registration of death may be delayed for several months.[23] Trends in mortality were analyzed using Kaplan-Meier survival analysis and Cox regression, comparing overall and overdose mortality by sex, age group, and route of administration.

The standardized mortality ratio (SMR) was estimated separately for males and

females. The mortality rate by 5-year age groups from 15 to 59 years for London in 1999 was multiplied by the number of person-years at risk in the cohort in 5-year age groups to calculate the expected number of deaths. The SMR was estimated by dividing the total number of observed deaths by the total number of expected deaths. Confidence intervals (CIs) for females were estimated using exact Poisson methods as there were fewer than 10 deaths; for males, 95% confidence intervals were estimated as $\pm 1.96 * \sqrt{O/E}$ (where $O$ = observed deaths, and $E$ = expected number of deaths).[24]

## RESULTS

### Participation

We approached 25 specialist drug agencies to participate; 23 agreed, and 2 refused because of staffing. Project start delays to obtain ethical approval (and subsequent changes in agency staffing levels) meant that 8 specialist drug agencies failed to supply any details on their clients in the time available. In total, therefore, 15 drug agencies participated.

A total of 1,718 reports to the DMD were sent to the specialist drug agencies. The client records were missing for 705 subjects (41%), which varied considerably by agency. For example, 90% of reports from two low-threshold agencies without computerized systems were missing, and less than 10% were missing from a residential agency. Finally, of the 1,013 postcards sent to ONS, 132 (13%) could not be traced. There were insufficient details on the subject to match with the NHS Central Register, or perhaps a false name for the subject had been given to the agency.

The final cohort comprised 881 heroin users from 15 specialist drug agencies in London. The mean age was 28 years, with 376 (43%) younger than 25 years, 193 (22%) aged 25–29 years, and 312 (35%) aged 30 years and older. Of the sample, 76% were reported as injecting drug users, 74% were male, and 75% represented white ethnic groups (2% from black ethnic groups, 4% Indian/Pakistani ethnic groups, and 19% missing data). The sample was recruited from first reports to the Drug Misuse Database in 1997 (180, 20%), 1998 (352, 40%) and 1999 (349, 40%).

By sex, age, or route of administration, the traced sample was not statistically different from the cases that were not traced or from subjects whose client records were not found. There were no differences in the recruitment year between traced and nontraced subjects, but more of the missing cases had first been reported in 1997 (32% vs. 20%) compared to those that had been identified.

### Mortality Rate

The 881 subjects were followed from date of report until date of death or January 31, 2001, an average of 2.3 years (minimum 0.01 to maximum 4.07) and a total of 2,075 person-years. Over the follow-up period, 33 (3.7%) subjects died. The overall mortality rate of the cohort of heroin users was 1.61 (95% CI, 1.13 to 2.23) per 100 person-years (Table 1). Mortality was higher among males (1.83; 95% CI, 1.28 to 2.67), heroin users aged older than 30 years (2.56; 95% CI, 1.61 to 4.05) and heroin users who were injectors at first report (1.90; 95% CI, 1.35 to 2.74).

Differences in survival were assessed using Cox proportional hazard models (Table 2) (for all models, there was no evidence that the proportional hazards as-

**TABLE 1. Mortality rate of cohort of problem heroin users recruited from specialist drug agencies in London**

| | Sample | Number of dead | Percentage of dead | Person-years | Mortality rate per 100 person-years | |
|---|---|---|---|---|---|---|
| | | | | | Overall | 95% Confidence interval |
| Total | 881 | 33 | 3.7 | 2,075.37 | 1.61 | 1.13–2.23 |
| Sex | | | | | | |
| Male | 656 | 28 | 4.3 | 1,523.51 | 1.83 | 1.28–2.67 |
| Female | 225 | 5 | 2.2 | 551.86 | 0.91 | 0.37–2.19 |
| Age group, years | | | | | | |
| <25 | 376 | 8 | 2.1 | 906.85 | 0.88 | 0.44–1.75 |
| 25–29 | 193 | 7 | 3.6 | 461.14 | 1.53 | 0.73–3.18 |
| 30+ | 312 | 18 | 5.8 | 707.38 | 2.56 | 1.61–4.05 |
| Route at first report | | | | | | |
| Injecting | 673 | 30 | 4.5 | 1,564.84 | 1.90 | 1.35–2.74 |
| Noninjecting | 208 | 3 | 1.4 | 510.54 | 0.58 | 0.18–1.83 |

**TABLE 2. Cox proportional hazard ratio: univariate and adjusted analysis**

| | Univariate analysis | | Adjusted analysis | | |
|---|---|---|---|---|---|
| Covariate | Hazard ratio | (95% CI) | Hazard ratio | (95% CI) | Number |
| Route of administration | | | | | |
| Injection* | 1 | | 1 | | 673 |
| Noninjection | 0.3 | (0.09 to 0.99) | 0.46 | (0.11 to 1.90) | 208 |
| Sex | | | | | |
| Male* | 1 | | 1 | | 656 |
| Female | 0.48 | (0.19 to 1.25) | 0.54 | (0.21 to 1.41) | 225 |
| Age, years | | | | | |
| <25* | 1 | | 1 | | 376 |
| 25–29 | 1.75 | (0.63 to 4.83) | 1.22 | (0.39 to 3.78) | 193 |
| 30+ | 2.92 | (1.27 to 6.72) | 1.92 | (0.72 to 5.15) | 312 |

CI, confidence interval.
*Reference.

sumption had been violated). In univariate analysis, noninjectors, compared to injectors, had a statistically significant lower hazard (0.3; 95% CI, 0.09 to 0.99); older age groups had a higher hazard compared to heroin users younger than 25 years (statistically significantly different for those older than 30 years (2.92; 95% CI, 1.27 to 6.72). In the adjusted analysis, however, none of the differences reached statistical significance.

Table 3 shows the underlying cause of death. There were 17 (52%) deaths certified as from a heroin/methadone or opiate overdose; 4 (12%) were certified as from drug misuse, but with no mention of a specific drug; and 4 (12%) were certified as open verdicts with an unascertainable cause of death (*ICD-9* [*International Classification of Diseases, 9th Edition*] code 799.9, "other unknown and unspecified cause"). All of these 4 deaths had an open verdict following inquest, and no apparent cause for the deaths were found at postmortem. There were 8 (24%) deaths unrelated to overdose or the acute effects of drug use, although some were clearly due to the late effects of injecting drug use (hepatitis C virus).

**TABLE 3. Underlying cause of death on death certificates**

| Cause of death | Number | Percentage (%) |
|---|---|---|
| Overdose mentioning heroin/methadone | 9 | 27 |
| Overdose, opiate | 8 | 24 |
| Drug misuse, no mention of specific drug | 4 | 12 |
| Unascertained | 4 | 12 |
| Liver/hepatitis C virus | 3 | 9 |
| Injury | 2 | 6 |
| Other* | 3 | 9 |
| Total | 33 | 100 |

*Other causes were heart disease (1), bronchopneumonia (1), meningitis (1).

If we assume that the certified deaths due to drug misuse and that the deaths due to unascertained cause were due to overdose, then there were potentially 25 (76%) overdose deaths, of which 17 (68%) would be recognized as an opiate-related death.[25] Table 4 shows the overdose mortality rate with deaths that mention opiates or drug dependence as a minimum estimate and includes the unascertained deaths as a maximum estimate. Overall, the overdose mortality rate ranged from 1.02 to 1.21 per 100 person-years and was higher among heroin users older than 30 years (1.42 to 1.68 per 100 person-years) and injectors (1.13 to 1.39 per 100 person-years). The adjusted hazard ratios were not significant, and both the univariate and adjusted ratios were similar to those in Table 2 (data not shown).

The mortality rates of the cohort are also seen in the Figure, which shows Kaplan-Meier survival curves by route of administration and for injectors by sex and age group. Thus, after 3 years, 6% (95% CI, 4.4% to 9.4%) of injectors died; this was 7% (95% CI, 4.6% to 10.2%) for male injectors, 5% (95% CI, 1.7% to 14.3%) for female injectors, and 8% (95% CI, 4.9% to 12.6%) for injectors aged 30 years or older.

### Standardized Mortality Ratio

Table 5 shows the estimation of the SMR comparing the cohort of problem heroin users and injectors with the mortality rate of males and females in London in 1999 standardized by 5-year age groups. The mortality rate among the cohort of female heroin users was over 17 (95% CI, 10 to 28) times higher than the mortality rate among the general female population of London. The SMR was 16.8 (95% CI, 11 to 23) for the male cohort of heroin users.

## DISCUSSION

### Feasibility

The pilot study showed that an anonymous drug treatment reporting system could be used as a sampling frame to monitor drug-related mortality. Specialist drug agencies agreed to participate; a sample of heroin users was recruited and successfully flagged with the ONS, and we gained approval from the drug agencies and ethical committees. We discuss the credibility and implications of the study findings and ethical considerations below.

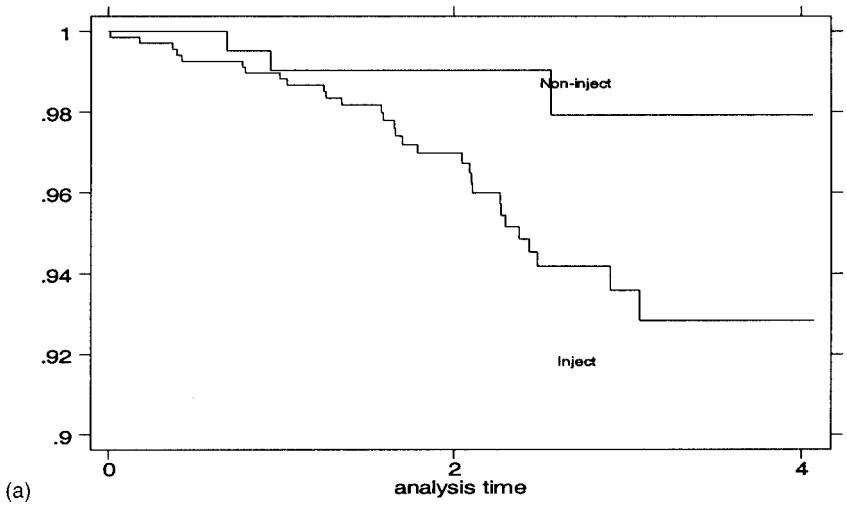
There were problems, however, with establishing the cohort retrospectively. Fewer agencies were recruited into the study than initially planned. Many agencies, although willing to undertake the study, were unable to participate fully because of a lack of staff or because of the unavailability of historic client records. Future studies would do better to recruit subjects prospectively or, if pursuing a retrospective cohort, select agencies with accurate record keeping.

Future cohort studies should be large and involve comparatively short follow-up periods rather than vice versa. Ongoing surveillance of drug-related mortality needs to establish whether it is higher than expected (e.g., an overdose mortality rate of 1.2% rather than 0.8%). In addition, to detect changes over time (e.g., a 20% decline in mortality), larger studies are needed (of the order of over 4,000–5,000 cases) to be recruited periodically over time. Short follow-up periods are required to avoid biases to the at-risk population (see below).

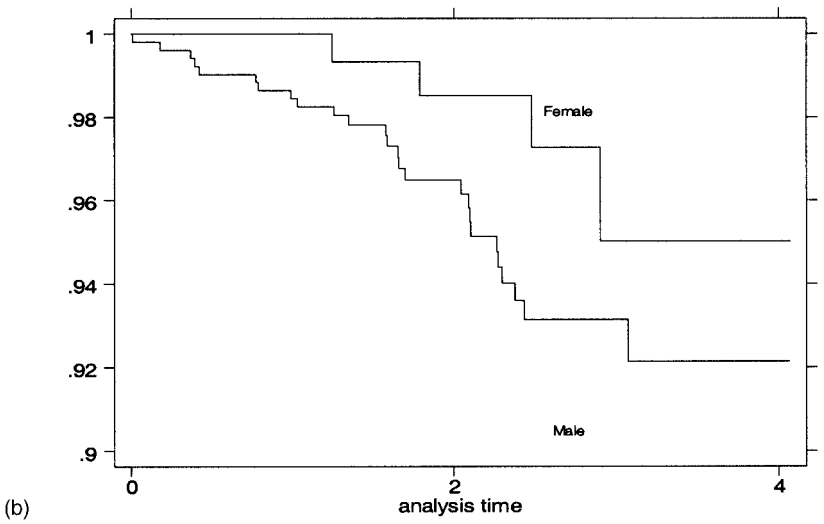
**TABLE 4. Opiate overdose mortality rate and mortality rate for overdose plus unascertained deaths**

| | | Overdose deaths | | | | Overdose rate per 100 person-years | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total | Minimum* | % | Maximum† | % | Minimum* | 95% CI | Maximum† | 95% CI |
| Total | 881 | 21 | 2.4 | 25 | 2.8 | 1.02 | 0.66–1.53 | 1.21 | 0.80–1.79 |
| Sex | | | | | | | | | |
| Male | 656 | 16 | 2.4 | 20 | 3.0 | 1.06 | 0.66–1.72 | 1.31 | 0.84–2.05 |
| Female | 225 | 5 | 2.2 | 5 | 2.2 | 0.91 | 0.37–2.19 | 0.91 | 0.37–2.19 |
| Age group, years | | | | | | | | | |
| <25 | 376 | 7 | 1.9 | 7 | 1.9 | 0.77 | 0.37–1.61 | 0.77 | 0.37–1.61 |
| 25–29 | 193 | 4 | 2.1 | 6 | 3.1 | 0.88 | 0.33–2.30 | 1.31 | 0.58–2.89 |
| 30+ | 312 | 10 | 3.2 | 12 | 3.8 | 1.42 | 0.77–2.63 | 1.68 | 0.95–3.00 |
| Route | | | | | | | | | |
| Injection | 673 | 18 | 2.7 | 22 | 3.3 | 1.13 | 0.73–1.83 | 1.39 | 0.91–2.12 |
| Noninjection | 208 | 3 | 1.4 | 3 | 1.4 | 0.58 | 0.18–1.83 | 0.58 | 0.18–1.83 |

CI, confidence interval.
*Opiate overdose deaths.
†Opiate overdose deaths plus unascertained deaths.




(a)

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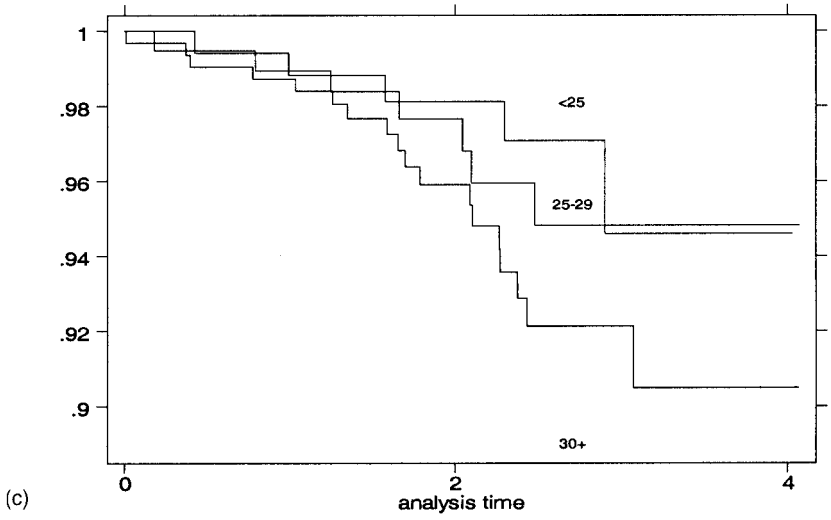


(c)

**FIGURE.** Kaplan-Meier survival curves of overall mortality of heroin users by (a) route of administration, (b) sex, and (c) age group.

**TABLE 5. Standardized mortality ratio (SMR) of problem heroin users compared to general population in London (aged 15–59 years)**

| | Population (15–59 years) | Number of deaths | Death rate per 1000 | Cohort sample | Mean follow-up, yrs | Cohort deaths | Expected deaths* | SMR | 95% CI |
|---|---|---|---|---|---|---|---|---|---|
| Females | 2,290,000 | 2,865 | 1.25 | 225 | 2.45 | 5 | 0.28 | 17.7 | 10–28 |
| Males | 2,370,000 | 4,964 | 2.09 | 656 | 2.32 | 28 | 1.67 | 16.8 | 11–23 |

CI, confidence interval.
*Expected deaths over cohort follow-up period, adjusted for 5-year age intervals.

## Results

Other potential biases are associated with cohort studies that do not have active follow-up and that recruit subjects from specialist treatment agencies. First, there is no follow-up of drug use or injecting status at the end of the study or of those switching from noninjecting to injecting routes of administration. This means that the overall number of person-years at risk did not take account of heroin users, especially injectors, who cease drug use, which over time may dilute and underestimate the drug-related mortality rate.[26] In addition, as noninjectors tend to switch at a higher rate to injecting than vice versa, over time the true difference in mortality by route will be diminished.[27] However, because the average follow-up in the study was 2 years, such a bias will be small.

Second, treatment is protective,[28,29] which means the estimates may underestimate the true mortality rate of heroin users, even though a significant proportion of the subjects reported to the DMD do not attend long enough to receive substitution treatment, and less than half of them will be in treatment after 1 year.

Nevertheless, the findings are plausible and serve to emphasize the public health importance of drug-related mortality and the reduction of overdose and drug-related deaths among heroin and injecting drug users. The study estimated the overall morality rate of a cohort of heroin users as 1.6 per 100 person-years and mortality from overdose as at least 1.0 per 100 person-years for heroin users recruited and followed-up from 1997 to 2001. The overall mortality was 1.9 per 100 person-years among those reporting injecting heroin at the beginning of the cohort. The study lends support to the hypothesis that the risk of death and overdose increases with age, and that it is not constant over time as has been previously suggested.[30,31]

The overall mortality rate for injectors was similar to that of a study in Glasgow, Scotland (1.8%), and an earlier London study (1.8%), although both of these studies followed a smaller number of subjects for a longer period: 459 subjects for 5.5 years and 128 subjects for 22 years, respectively.[12,14] Mortality was higher in this study than the National Treatment Outcome Research Study, for which the annual rate was 1.2%, and the most recent study based on the Addicts Index,[20,32] which estimated overall mortality as 1.05 per 100 person-years for opiate addicts notified from 1984 to 1993. Overdose mortality was slightly higher than the meta-analysis estimates of 0.8% per annum.[4]

The study suggested that the mortality rate among problem heroin users was 17 times higher for females and males compared to the general population aged 15–59 years in London. Compared to other studies, these SMRs were similar to those for females (18.1), but higher than for males (9.3) in Rome, Italy[13]; lower than for females (37.7) and similar to those for males (16.1) in Glasgow[12]; higher than for females (13.9) and males (11.2) in the study of Oppenheimer et al. in London[14]; and higher than for females (7.0) and males (10.0) in a UK study using the Addicts Index.[20] The SMR was also higher than the general estimate of 13 times given by Hulse et al.[4] and higher than the estimate given by Gossop and colleagues[32] (6 times), which was not age adjusted.

Finally, the analysis highlights the importance of cohort studies as part of public health surveillance of overdose and drug-related mortality. Over half of the 33 deaths identified in the pilot were classified as deaths from heroin, methadone, or opiate overdose. An additional 4 deaths were certified as due to drug misuse without specification, but were likely to be due to an overdose. Another unascertained 4 may also have been due to an overdose.

### Ethical Implications

Patient confidentiality was protected by limiting access to identifying information to the agency and ONS and restricting information on drug use to the agency and researchers. However, it is by no means certain that, under current data protection and confidentiality law, a retrospective study would be acceptable because patient consent could not and was not requested and provided. In the European Union (EU), data protection is governed by an EU directive, which has been implemented in the national law of all EU states. Its application to public health surveillance and research is not entirely clear.[33] The data protection law in the US health field is similarly complex.[34]

The weak point, on strict interpretation of the Data Protection Act, of this study design is perhaps the transfer of information between the agencies and the NHS Drug Misuse Database because consent for this information and research use was not obtained. It is impractical to obtain consent retrospectively from currently registered drug users. A prospective design with informed consent may confer certain epidemiological advantages by allowing a structured questionnaire, but would add significantly to the cost. However, we believe there is stronger public interest in supporting retrospective studies given that there is little or no current investment in cohort studies of heroin users to monitor overdose and drug-related mortality.[35]

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